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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,927	12/23/2004	Helmut Fiebig	MERCK-2966	8085

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,927	FIEBIG ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,16,21,22,26,30,31,33 and 35-38* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 16* is/are withdrawn from consideration.

5)☒ Claim(s) *13,15,26,33 and 35-38* is/are allowed.

6)☒ Claim(s) *21-22, 30-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/03/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed on 08/03/2010 is acknowledged.

2. Claims 1-13, 15-16, 21-22, 26, 30-31, 33 and 35-38 are pending.

3. Claims 1-12 and 16 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/29/2007.

4. Claims 13, 15, 21-22, 26, 30-31, 33 and 35-38 are currently under examination as they read on a polypeptide encoded by the nucleic acid sequence of SEQ ID NO:1 and a pharmaceutical composition thereof.

5. Applicant's IDS document filed on 08/03/2010 is acnowledged.

6. In view of Applicant's response filed on 08/03/2010, only the following rejections are maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 21-22 and 30-31 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: recombinant, isolated polypeptides of SEQ ID NO: 2, 4,

6 encoded by SEQ ID NO:1, 3 or 5, respectively, the variants of SEQ ID NO:2 in clones 1-11, the polypeptide fragments 1-200 and 185-500 thereof and a composition thereof, does not reasonably provide enablement for: an **immunomodulatory, T-cell-reactive polypeptide fragment which comprises a partial sequence of 50 to 350 amino acids** of the polypeptide sequence (set forth in of claim 13) of claim 21; a polypeptide fragment which **comprises** amino acids 1-200 or amino acids 185-500 of the polypeptide sequence set forth in SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO: 6 or a polypeptide variant of the sequence set forth in SEQ ID NO: 2 with the amino acid variations set forth in clones 1 to 11 of claim 22 and a **pharmaceutical composition** comprising at least one polypeptide according to Claim 21 or Claim 22 of Claims 30-31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons as set forth in the Office Action mailed on 05/03/2010.

Applicant's arguments filed on 08/03/2010 have been fully considered, but are not found persuasive.

Applicant argues:

> "With regard to the enabtement rejection, the Office Action contends that specification does not provide enablement for the fragment potypeptides recited in claim 22 and/or the functional activity of such partial sequences recited in claim 21. The Examiner further contends that the pharmaceutical preparations comprising such fragments or partial sequences are not enabled.
>
> Applicants remarks of December 28, 2009 are incorporated by reference in their entirety with regard to the sustained rejections under §112, ¶1."

It remains the Examiner's position that the specification does not provide support for any polypeptide fragment which "comprises" a partial sequence of 50 to 350 amino acids, amino

acids 1-200 or amino acids 185-500 of the recited sequences. The term 'comprises' is open language which opens the claim up to encompass an enormous number of undisclosed fragments which may include sequence added onto the N-and/or C-terminus that is unrelated to the polypeptides of SEQ ID NO:2, 4 or 6 or the variants of SEQ ID NO:2 in clones 1-11. The limitations of "an immunomodulatory, T-cell-reactive polypeptide fragment" of claim implies that the immune system is changed, but no specific changes are recited. Therefore, the term 'immunomodulatory' encompasses just about any reaction by any cells or pathways related to the immune system. In the same way, the term 'T-cell reactive' is largely undefined. Any fragment or processed subsequence of the fragment that induces any T cell response or interaction is encompassed by the instant claims. Without a recitation for a specific function of peptides which "comprise" the recited fragments, one of ordinary skill in the art would not be able to screen for peptides that possess the requisite function and which could be made and used in the claimed invention. Applicant's argument that the fragments could be further tested, for example, with respect to binding to monoclonal antibodies and/or IgE reactivity and that the whole process would constitute nothing beyond what is routine in the art and that the screening for T-cell and IgE epitopes were common knowledge at the priority date of the present application and a person skilled in the art would have been able to identify T-cell and IgE epitopes and produce hypoallergenic peptides is not persuasive. Without a recitation for the testable function in the claim, one of ordinary skill in the art would not be able to test the peptides for requisite activity to determine the genus of peptides encompassed for use in the claimed invention.

It is the Examiner's position that when a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use. See MPEP

2164.01(c). Following the guidance from the MPEP, for the claim to be enabled, the specification must teach how to make the claimed composition without undue experimentation and must teach how to use the composition for at least one pharmaceutical use without undue experimentation. To enable a pharmaceutical use for a substance, the specification must teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment, or cure a disease in the animal to which the substance is administered. When applicant is claiming a pharmaceutical composition, applicant must enable a pharmaceutical use. This rejection could be overcome by deleting the words "pharmaceutical" from the claim as when no use is recited in a claim, any enabled use will suffice.

The claims, as recited, include the use of SEQ ID NOs: 2, 4, or 6, the variants of SEQ ID NO:2 in clones 1-11, any polypeptide comprising amino acids 1-200, amino acids 185-500 and any 50 to 350 amino acid long peptide from SEQ ID NO: 2, 4, 6 or the variants of SEQ ID NO:2 in clones 1-11. It is well known in the art that even small changes can affect the binding specificity of an antibody. Colman *et al.* (PTO-892 mailed on 09/25/2009; Reference U) teaches that single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza et al. in (PTO-892 mailed on 09/25/2009; Reference V) teaches that single amino acid substitutions that are outside the antigenic site on a protein effect antibody binding. Further, Lederman *et al.* (PTO-892 mailed on 09/25/2009; Reference W) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). In addition, Blumenthal et al. teaches that correlations between structure and IgE binding (or the lack of IgE binding) cannot be predicted on an a priori structural basis (PTO-892 mailed on 09/25/2009, Reference X, see entire document and page 39 of third full paragraph). Kinnunen et

al. (PTO-892 mailed on 09/25/2009 page 2, Reference U, abstract, discussion) teaches that the use of allergen peptide derivatives or "altered peptide ligands" of the lipocalin allergen. The reference teaches that APL induce differential T cell stimulation (In particular, Table I, page 6, paragraph spanning left and right columns). The discussion cautions those who are looking to use APL in immunotherapy for allergy because some T cells populations, such as pathogenic memory cells, that are induced by certain APL would exacerbate allergic disease (In particular, page 7, left column, second paragraph). One of ordinary skill in the art would be required to determine how alterations to each position of the peptide affect binding to MHC and how that in turn effects T cell activation. The T cell activation induced by the peptide in vivo would need to promote hypoallergenic/ tolerogenic effects, which is also highly unpredictable. The specification has not adequately disclosed the genus of polypeptide fragments which comprise fragments of allergens and allergen variants to be used to treat allergy. The aforementioned unpredictibility in the art highlights that an undue amount of experimentation is necessary to practice the claimed invention.

Therefore, for all the reasons stated *supra*, it remains at issue is whether or not the claimed compositions would function as a 'pharmaceutical composition.' In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the pharmaceutical composition or vaccine as claimed, absence of working examples providing evidence which is reasonably predictive that the claimed pharmaceutical compositions are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

The Examiner does not know why Applicant is arguing about DNA vaccines, as the claims do not in any way encompass DNA vaccines.

Applicant's argument that Focke et al.(Focke et al., *FASEB Journal,* 15, 2042- 44, 2001), teaches that the instantly claimed grass pollen allergens could be routinely manipulated and utilized as pharmaceutical preparations in a manner recited in the claims is confusing and not persuasive. First, Focke et al. is directed to Phl p1, not Phl p 4 as presently claimed so the Examiner is not sure why Applicant stated that it is directed to the instantly claimed grass pollen allergens. Further, the reference teaches in vitro and in vivo skin assays using 28-32 amino acid long peptides of Phl p 1. The reference does not teach using longer peptides as claimed, nor does the reference teach using peptides that comprise non-allergen amino acids on their N- and/or C-terminus as the claims encompassed by the instant claim recitations. This reference would be persuasive to show that small peptides consisting of a recited sequence that have the function of being able to generate protective IgG antibodies that inhibit the binding of IgE to the native allergen for pharmaceutical use. However, the instant claims are not directed to what is routine in the art of Focke et al.

Applicant's assertion that that the assertion of undue experimentation is merely conclusory is not persuasive. The Examiner has provided sufficient reasoning to question the enablement set forth in the specification for the genus of peptides and pharmaceutical compositions encompassed. The claims with "comprising" language that read on less than full length require a recitation of a testable function. The Examiner has shown above and in previous Office Actions that protein function and IgE binding are impacted by structure and that one cannot predict how changes in structure will alter antibody binding and protein function. As

such, using the genus of peptides encompassed in a pharmaceutical composition to treat allergy is unpredictable and would require one of ordinary skill in the art to perform undue experimentation to practice the invention commensurate in scope with the claims. Accordingly, the rejection of claims 21-22 and 30-31 is maintained.

9. Claim 21 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : recombinant, isolated polypeptides of SEQ ID NO: 2, 4, 6 encoded by SEQ ID NO:1, 3 or 5, respectively, the variants of SEQ ID NO:2 in clones 1-11, the polypeptide fragments 1-200 and 185-500 thereof and a composition thereof

Applicant is not in possession of : an **immunomodulatory, T-cell-reactive polypeptide fragment which comprises a partial sequence of 50 to 350 amino acids** of the polypeptide sequence (set forth in of claim 13) of claim 21 for the same reasons as set forth in the Office Action mailed on 05/03/2010.

Applicant's arguments filed on 08/03/2010 have been fully considered, but are not found persuasive.

> "With regard to the written description rejection, Applicants submit that in view of the Examiner's arguments at page 9 of the Office Action, the subject matter of claims 13 and 22, including newly added claims 37 and 38 is adequately described."
>
> Applicants remarks of December 28, 2009 are incorporated by reference in their entirety with regard to the sustained rejections under §112, ¶1."

It remains the Examiner's position that to satisfy the Written Description requirement, Applicant must describe a correlation between the structure and the function. If no function is recited in the claims (as in claim 22), then it is *possible* that the claims satisfy the written description requirement, while not satisfying the enablement requirement which requires the recitation of a testable function in order to make and use.

It remains the Examiner's position that the specification has not adequately disclosed the genus of polypeptide variants fragment comprises a partial sequence of the disclosed polypeptides wherein the polypeptide fragments have a function (immunomodulatory and T-cell reactive). It remains the Examiner's position that the specification does not disclose a correlation between the structure of the allergens, variants and fragments thereof and function ("immunomodulatory, T-cell-reactive" of claim 21) such that a skilled artisan would have known what allergen variants and fragments of the Phl p 4 allergens attain the claimed functions. "Possession may not be shown by merely describing how to obtain possession of member of the claimed genus or how to identify their common structural features" *Ex parte Kubin* (83 U.S.P.Q.2d 1410 (BPAI 2007)), at page 16. "Without a correlation between structure and function, the claim does little more than define the claimed invention by function" *supra*, at page 17. Definition by function does not suffice to define the genus because it is only an indication of what the allergen does and what functional properties it has, rather than what it is.

Accordingly, the rejection of claim 21 is maintained.

10. Claims 13, 15, 26, 33 and 35-38 appear to be in condition for allowance.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 12, 2010

/Nora M Rooney/
Primary Examiner, Art Unit 1644